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APPLICATION OF	:	Kohn, *et al.*
SERIAL NO.	:	08/225,478
FILED	:	April 8, 1994
FOR	:	Gene Therapy by Administration of Genetically Engineered CD34+ Cells Obtained From Cord Blood
GROUP	:	1804
EXAMINER	:	Milne

#25
D.J.
3/26/97
(NE)

Assistant Commissioner of Patents
Washington, DC 20231

SUPPLEMENTAL RESPONSE

SIR:

This is a Supplemental Response to the Notice of Appeal filed on December 6, 1996.

Subsequent to the filing of the Notice of Appeal, Applicants' attorneys, Elliot M. Olstein and Raymond J. Lillie, engaged the Examiner and his supervisor, Examiner Jacqueline Stone, in a series of telephone interviews on December 6, 1996, January 17, 1997, February 5, 1997, and February 12, 1997. Such interviews are noted with appreciation to Examiners Milne and Stone. During such interviews, issues relating to the rejection under 35 U.S.C. 112, first paragraph, were discussed. During the interviews, the Examiners suggested to Applicants' attorneys that they provide a declaration which would indicate that experimental results described in certain publications describing the claimed invention can be interpreted as indicating that CD34+ cells obtained from cord blood, which have been genetically engineered to include at least one nucleic acid sequence encoding a therapeutic agent, express the therapeutic agent in amounts sufficient to provide a therapeutic effect.

Accompanying this supplemental response is a declaration under 37 CFR 1.132 of Donald B. Kohn, one of the inventors of the claimed subject matter of the above-identified application. In such declaration, Dr. Kohn testifies that he is a co-author of Kohn, et al., Nature Medicine, Vol. 1, No. 10, pgs. 1017-1023 (October 1995), which is attached to the declaration as Exhibit 1.

Dr. Kohn then testifies that CD34+ cells were isolated from the cord blood of a newborn infant patient diagnosed with adenosine deaminase (ADA) deficiency. The isolated CD34+ cells were transduced with the retroviral vector LASN, which includes DNA encoding normal human adenosine deaminase under the control of a Moloney Murine Leukemia Virus LTR and a neomycin resistance gene under the control of an SV40 promoter. The transduced CD34+ cells then were returned to the patient by intravenous infusion. At age 18 months, CD34+ bone marrow cells were isolated from the patient and selected for G418 resistance. Cells that were found to be G418 resistant were grown in culture for two weeks.

Dr. Kohn also testifies that CD34+ cells from the bone marrow of a normal donor were transduced with the retroviral vector LN, which includes a neomycin resistance gene under the control of the Moloney Murine Leukemia Virus LTR. These cells then were cultured in the presence of G418 to select for G418 resistance.

The cells obtained by culturing selected G418 resistant CD34+ cells obtained from the patient, and the G418 resistant cells obtained from a normal donor, were evaluated for expression of adenosine deaminase. 24,051.0 nmol of ADA per hour per mg of protein was expressed by the cells in the culture obtained by culturing G418 resistant CD34+ cells obtained from the patient. 4,694.0 nmol of ADA per hour per mg of protein was expressed by the LN vector transduced cells obtained from the bone marrow of the normal donor.

Dr. Kohn testifies that, in his opinion, the above-mentioned results show that the level of ADA produced by the LASN vector transduced CD34+ cells from the patient is similar to that of a normal person, and therefore, such results provide evidence, although indirect, that the patient's cells which include the LASN vector are expressing ADA at levels sufficient to provide a therapeutic effect.

Dr. Kohn also testifies that he also is a co-author of an abstract by Kohn, et al., entitled "Selective Accumulation of ADA Gene-Transduced T-Lymphocytes Upon PEG-ADA Dosage Reduction after Gene Therapy with Transduced CD34+ Umbilical Cord Blood Cells." The article was published in Blood, Vol. 86 No. 10, Supp. 1 (November 15, 1995), and is attached to the Declaration as Exhibit 2. Dr. Kohn states that the abstract describes the infusion of three newborn infant patients diagnosed with ADA deficiency with autologous umbilical cord blood CD34+ cells that had been transduced with the retroviral vector LASN. Each of the three

patients also received PEG-ADA in an amount of 60 units per kilogram per week. Dr. Kohn then states that, at 18 months of age, the dosage of PEG-ADA for each patient was reduced to 20 to 30 units per kilogram per week. Dr. Kohn testifies that those skilled in the art, when treating ADA deficiency, administer PEG-ADA to a patient in an amount of at least 30 units per kilogram per week to about 60 units per kilogram per week in order to achieve a therapeutic effect in the patient. Dr. Kohn also states that after lowering the dosage of PEG-ADA to 20 to 30 kilograms per week in each patient, that each patient remained in good health and no changes in the clinical conditions of the patients were observed.

Dr. Kohn testifies further that subsequent to the publication of Exhibit 2, and at 30 months of age, the dosage of PEG-ADA administered to one of the patients was lowered to 15 units per kilogram per week. After lowering the dosage of PEG-ADA to 15 units per kilogram per week in one of the patients, such patient remained in good health and no changes in the clinical condition of the patient were observed.

Thus, the accompanying declaration provides evidence, although indirect, which shows that autologous CD34+ cells may be genetically engineered with a nucleic acid encoding a therapeutic agent, and that such cells may be returned to the patient, whereby the cells produce the therapeutic agent in the patient in an amount effective to provide a therapeutic effect. Therefore, for the above reasons and others, Applicants have demonstrated that the claimed invention is enabled, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn and an early notice of allowance is hereby solicited.

Respectfully submitted,

Raymond J. Lillie 3/5/97

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